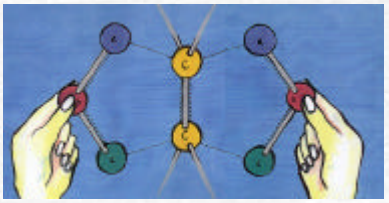

New Catalytic Asymmestric Reactions

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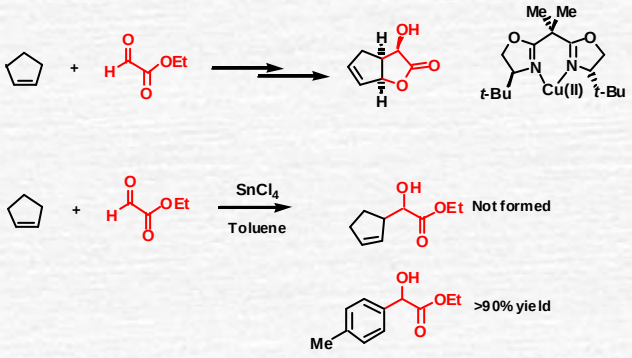
DANMARKS GRUNDFORSKNINGSFOND
DANISH NATIONAL RESEARCH FOUNDATION

When something goes wrong

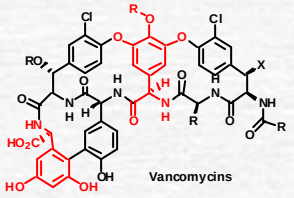
Goya: *Mother showing her derformed child to two women*
Louvre, Paris

A failed reaction

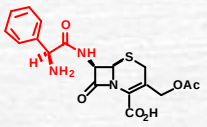


Chem. Commun. **1999**, 1869

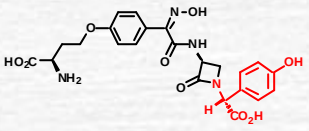
Catalytic asymmetric aza-Friedel-Crafts reactions



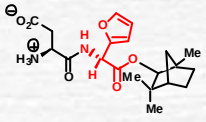
Vancomycins



Cephaloglycin

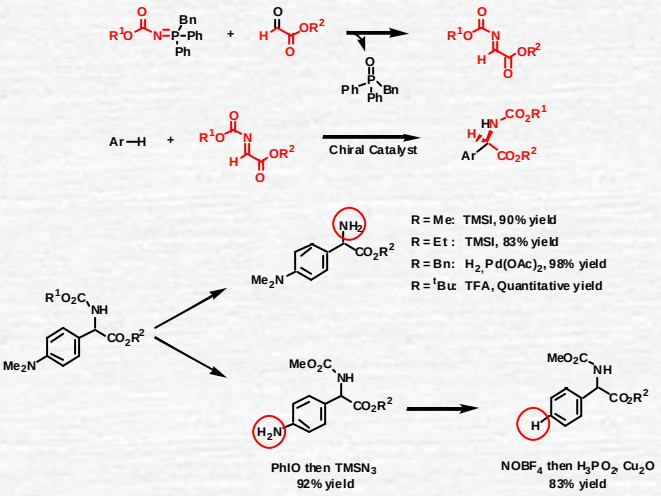


Nocardicin A



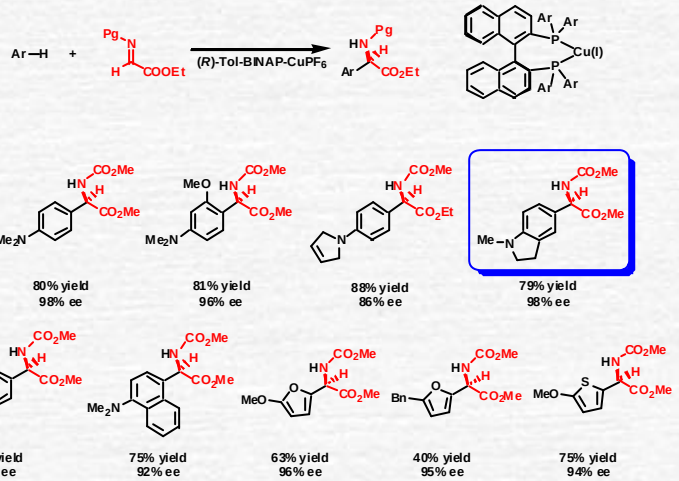
Aspartame analogue

Optically active aromatic a -amino acids

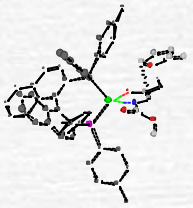


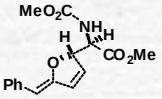
Angew. Chem. Int. Ed. **2000**, *39*, 4114
J. Org. Chem. **2002**, *67*, 4352

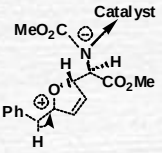
Scope and potential

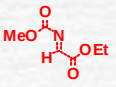


Mechanistic Considerations

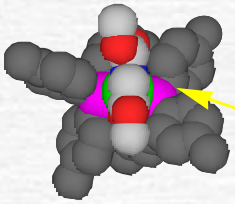


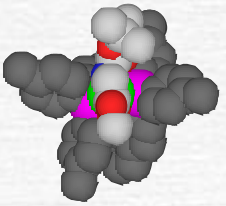


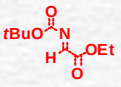




High Discrimination

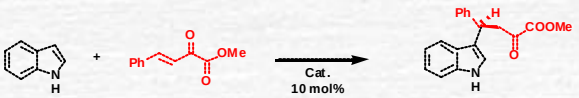


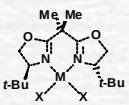


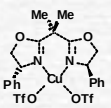


Low discrimination

Catalytic asymmetric Friedel-Crafts alkylation reactions



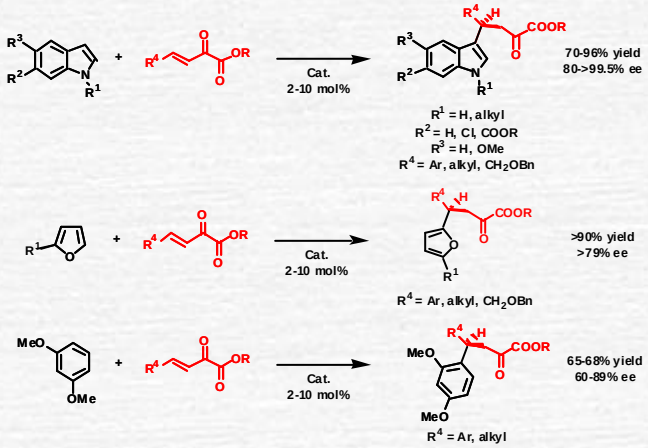




M = Cu(II), X = OTf (CH_2Cl_2): 100% conversion, 88% ee
M = Cu(II), X = OTf (Et_2O): 100% conversion, 97% ee
M = Zn(II), X = OTf (CH_2Cl_2): 100% conversion, 87% ee

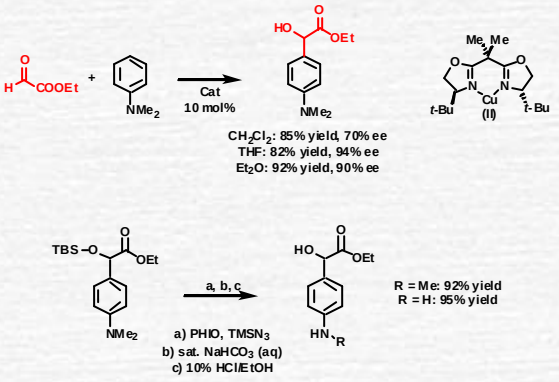
100% conversion, 42% ee

Angew. Chem. Int. Ed. **2001**, *41*, 160



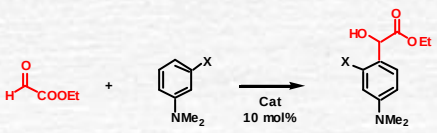
Catalytic enantioselective Friedel-Crafts reactions

a simple approach to optically active α-aromatic α-hydroxy carboxylic acids

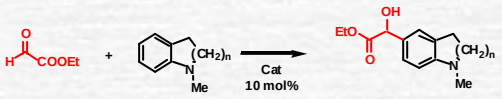


J. Am. Chem. Soc. **2000**, *122*, 12517
J. Org. Chem. **2001**, *66*, 1009

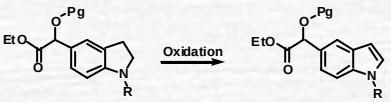
Scope and potential



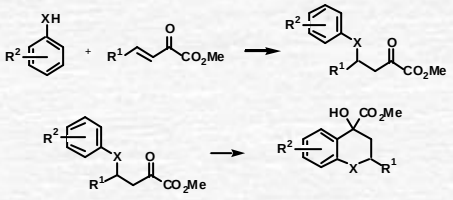
>80 yield , >85% ee

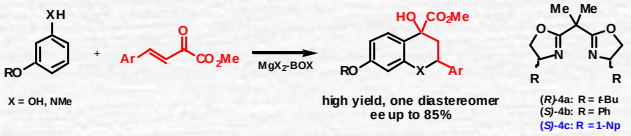


n = 1: 54% yield, 85% ee
n = 2: 56% yield, 93% ee



Catalytic asymmetric tandem reactions – formation of optically active dihydro-benzopyrans





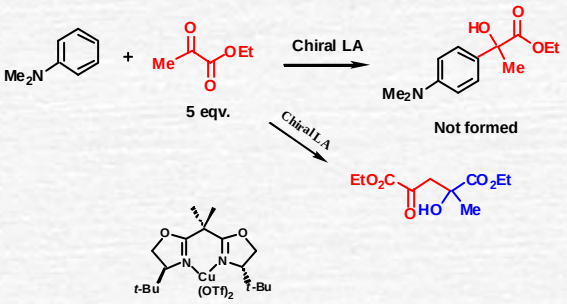
X = OH, NMe

high yield, one diastereomer
ee up to 85%

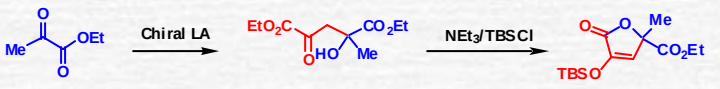
(*R*)-4a: R = *t*Bu
(*S*)-4b: R = Ph
(*S*)-4c: R = 1-Np

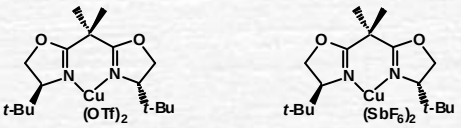
Submitted **2002**

Discovery of a direct aldol reaction



A catalytic asymmetric homo-aldol reaction



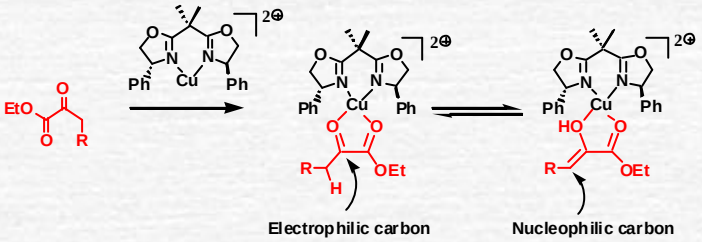


Amine [mol%]	Ee [%]
-	(–)-65
$PhNMe_2$/10	(–)-79
$PhNMe_2$/5	**(–)-96**
$PhNBn_2$/10	(–)-93
$Et(^iPr)_2N$/10	(–)-67

Amine [mol%]	Solvent	Ee [%]
-	Et_2O	(–)-50
$PhNMe_2$/10	CH_2Cl_2	(+)-63
$PhNBn_2$/10	CH_2Cl_2	(+)-75
$CyNMe_2$/10	CH_2Cl_2	**(+)-77**

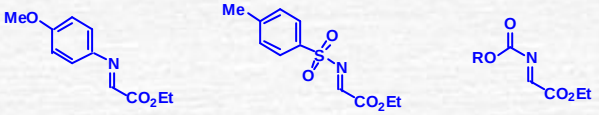
Chem. Commun. **2000**, 2211

The concept



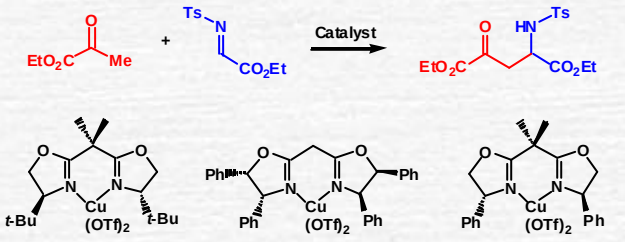
Catalytic asymmetric direct Mannich reactions

Imine candidates



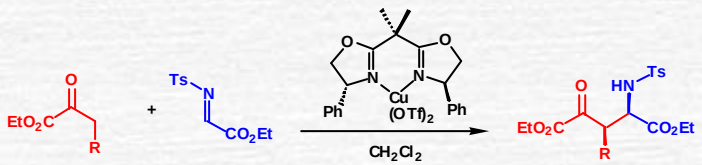
Angew. Chem. Int. Ed. **2001**, *40*, 2995

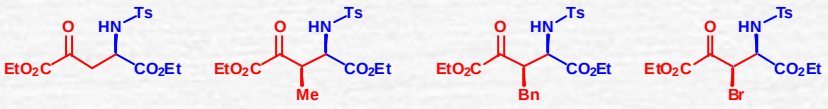
Optimisation of the direct Mannich reaction



CH_2Cl_2	CH_2Cl_2	THF	CH_2Cl_2	THF
76% yield	44% yield	16% yield	70% yield	45% yield
-33% ee	12% ee	33% ee	89% ee	76% ee

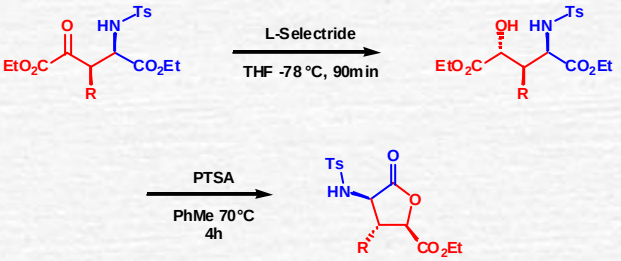
Scope of the direct Mannich reaction





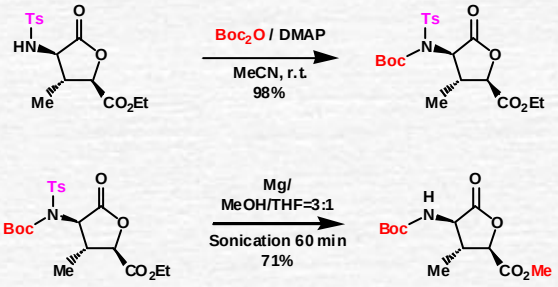
70% yield	89% yield	94% yield	79% yield
89% ee	>10:1 dr	>10:1 dr	3:1 dr
	>98% ee	97% ee	78% ee

Reduction of the Mannich product

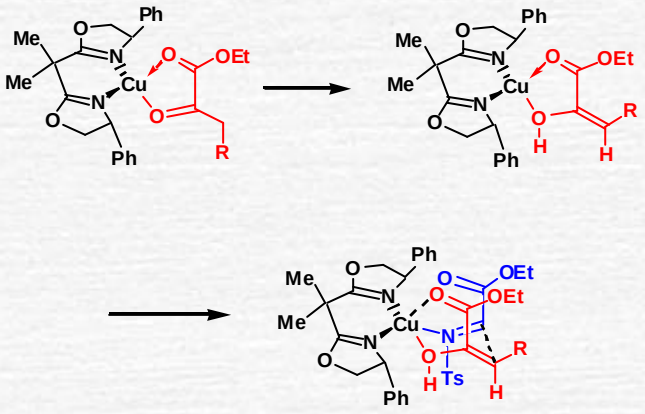


R = Me: 92% yield
one diastereomer
R = Bn 70% yield
one diastereomer

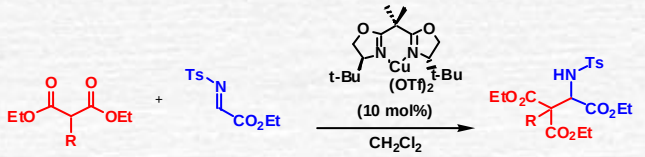
Detosylation



Proposed Mechanism

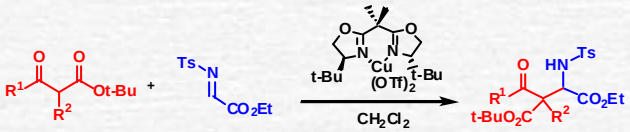


Malonic esters and β-keto esters as nucleophiles in direct Mannich reactions



R = Me, *n*-Bu, *i*-Bu, Bn

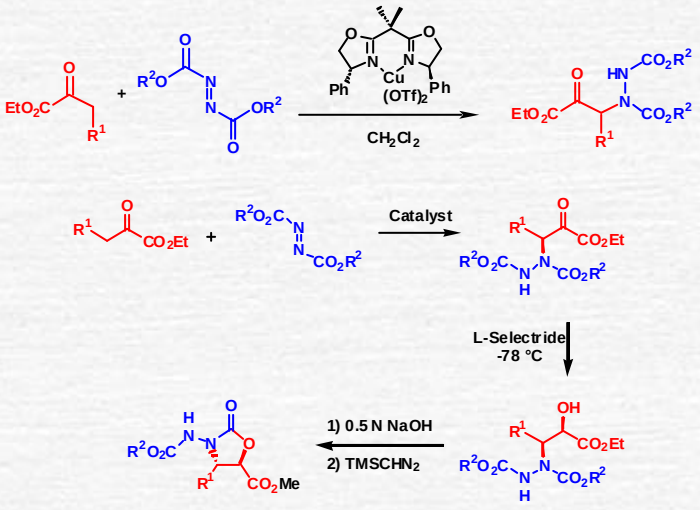
Yields: >80%; >85% ee



$R^1 = R^2$ = Me: 87%, 93:7 dr, 88% ee
R^1 = Et, R^2 = Me: 80%, 98:2 dr, 92% ee
R^1 = *i*-Pr, R^2 = Me: 55%, 84:16 dr, 91% ee
R^1 = Bn, R^2 = Me: 83%, 96:4 dr, 93% ee
R^1 = Me, R^2 = allyl: 69%, 92:8 dr, 87% ee
$R^1 = R^2 = (CH_2)_4$: 89%, 99:1 dr, 86% ee

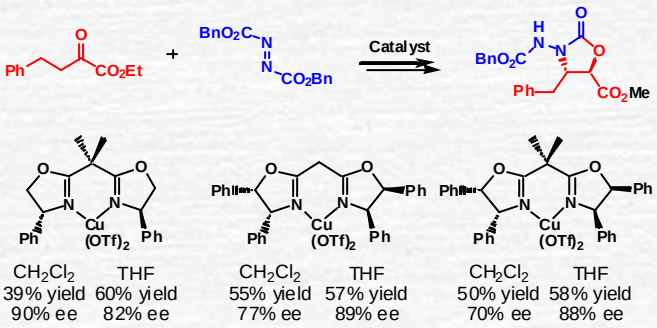
Submitted for publication

Catalytic asymmetric direct α-amination

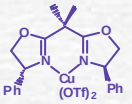


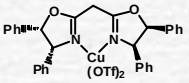
J. Am. Chem. Soc. **2002**, *124*, 2420

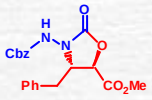
Optimisation of the direct α-amination reaction



Scope of the direct a -amination reaction

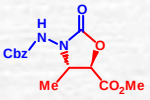




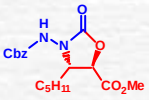


CH_2Cl_2 39% yield 90%ee

THF 57% yield 89%ee

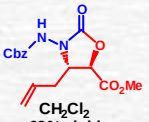


CH_2Cl_2 45% yield 90%ee

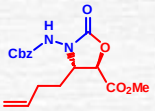


CH_2Cl_2 78% yield 92%ee

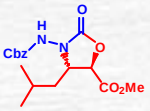
CH_2Cl_2 48% yield 97%ee



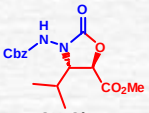
CH_2Cl_2 62% yield 93%ee



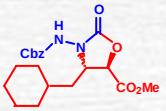
CH_2Cl_2 52% yield 92%ee



CH_2Cl_2 53% yield 96%ee

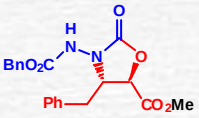


CH_2Cl_2 78% yield 95%ee



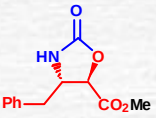
THF 72% yield 96%ee

Synthesis of oxazolidinones

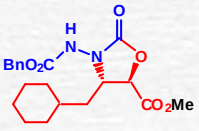


1) Pd/C H_2 MeOH

2) Zn acetone HOAc

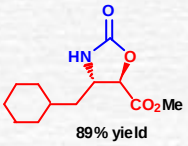


88% yield



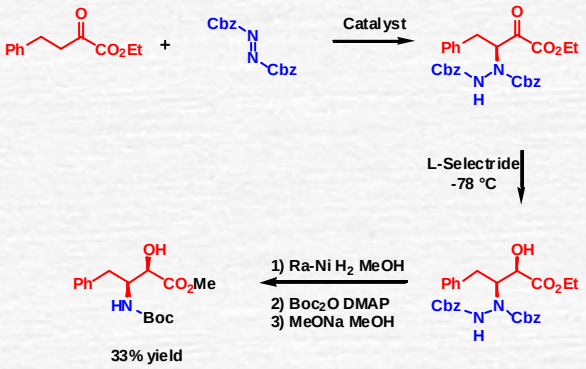
1) Pd/C H_2 MeOH

2) Zn acetone HOAc

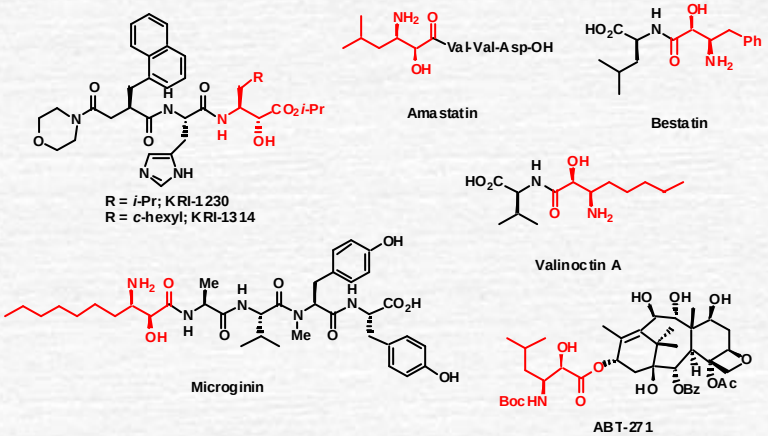


89% yield

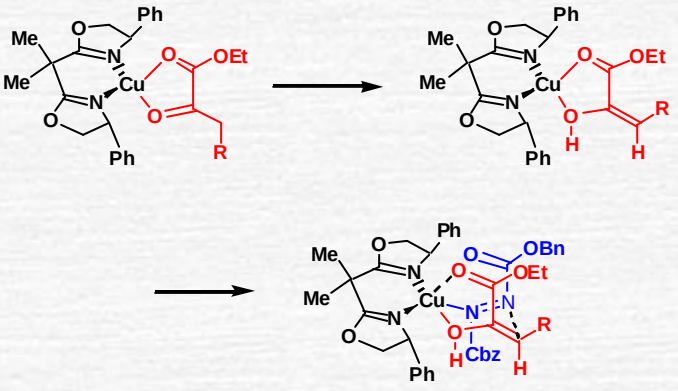
Synthesis of *syn*-a-hydroxy-b-amino acids



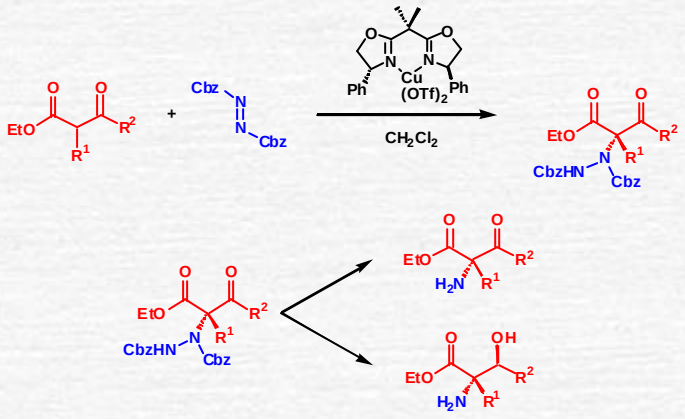
33% yield



Proposed mechanism

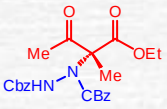


Catalytic asymmetric direct α-amination of β-keto esters – optically active β-keto- and β-hydroxy-α-amino acids



Submitted for publication

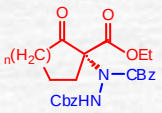
Scope



81% yield, 98% ee

94% yield, 98% ee

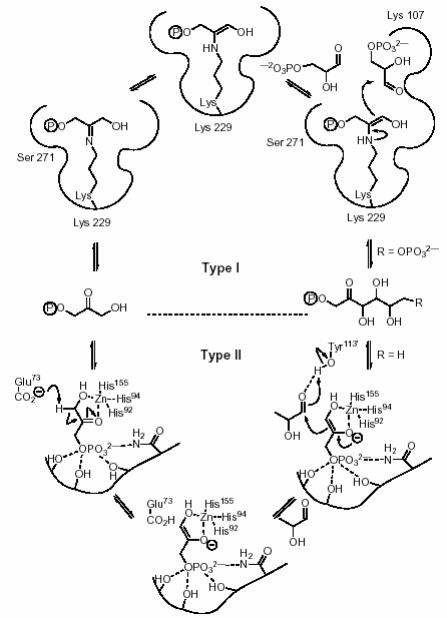
88% yield, 98% ee



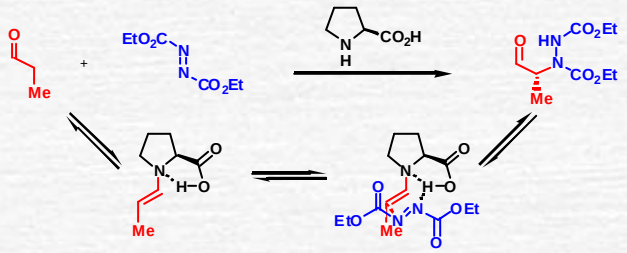
n = 1: 99% yield, 99% ee
n = 2: 94% yield, 98.5% ee
n = 2: 92% yield, 98% ee

Organo Catalytic Aldol Reaction: Type I Aldolase

Metal Catalysed Aldol Reaction: Type II Aldolase



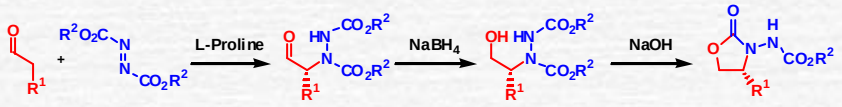
L-Proline catalysed asymmetric a -amination of aldehydes

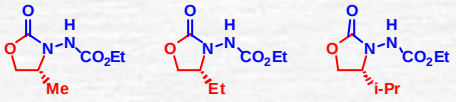


Solvent	L-Proline (mol%)	Reaction time [min]	Yield [%]	ee [%]
CH_2Cl_2	50	45	93	92
CH_2Cl_2	5	105	87	91
CH_2Cl_2	2	300	92	84
MeCN	50	30	70	91
EtOAc	50	300	77	81
PhMe	50	450	81	86

Angew. Chem. Int. Ed. **2002**, *41*, 1790 (rec. 01.03.02)
List, *J. Am. Chem. Soc.* **2002**, *124*, 5656 (rec. 07.03.02)

Scope of the L-proline catalysed asymmetric a -amination of aldehydes

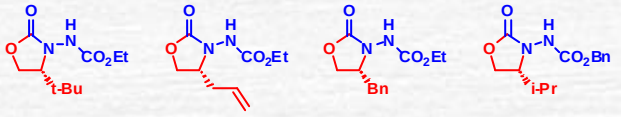




Yield 67%
ee 93%

Yield 77%
ee 95%

Yield 83%
ee 93%



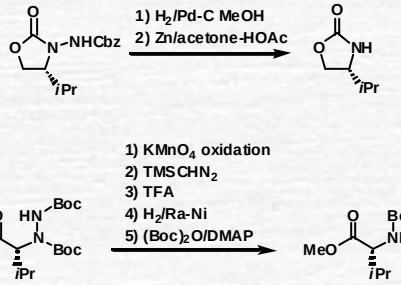
Yield 57%
ee 91%

Yield 92%
ee 93%

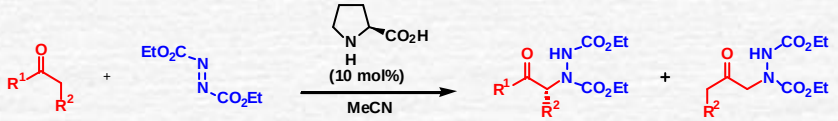
Yield 68%
ee 89%

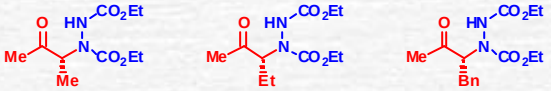
Yield 70%
ee 91%

Product modification / Determination of absolute configuration



L-proline catalysed asymmetric a - amination of ketones

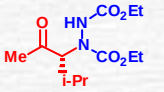




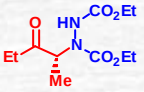
Regioselectivity: 91:9
Yield: 80%
ee: 95%

Regioselectivity: 81:19
Yield: 77%
ee: 98%

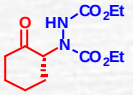
Regioselectivity: 82:18
Yield: 92%
ee: 95%



Regioselectivity: 76:24
Yield: 69%
ee: 99%



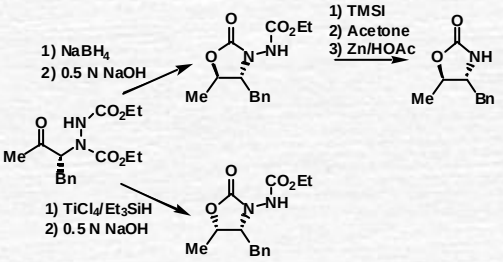
Yield: 79%
ee: 94%



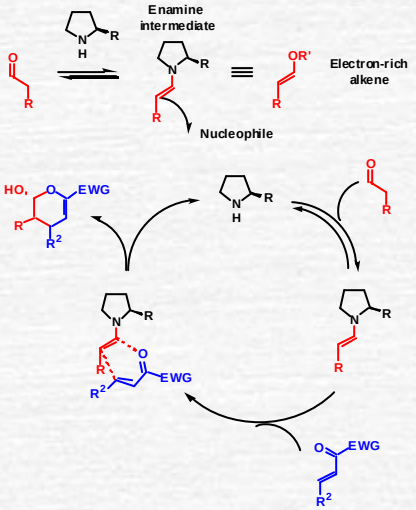
Yield: 67%
ee: 84%

J. Am. Chem. Soc. **2002**, *124*, 6254

Stereoselective formation of optically active oxazolidinones

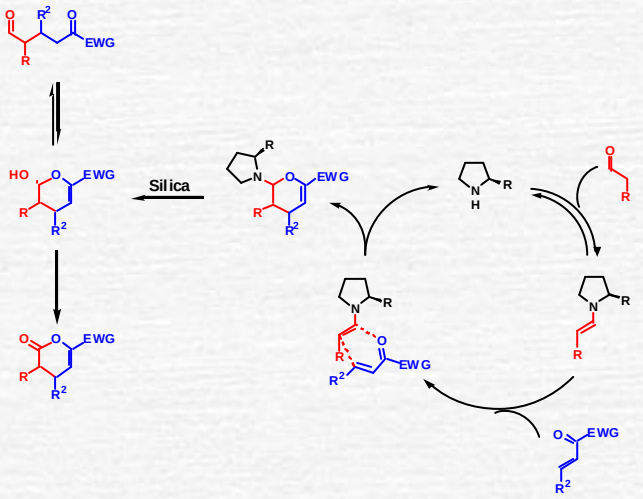


The first organo-catalytic inverse-electron demand hetero-Diels-Alder reaction – direct evidence for enamine intermediate

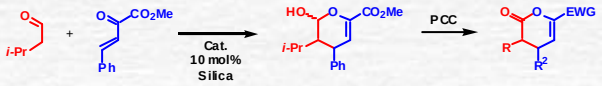


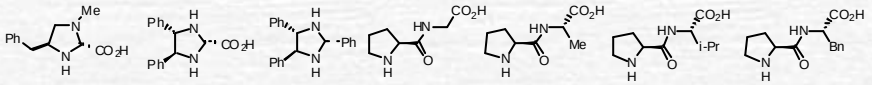
Submitted for publication

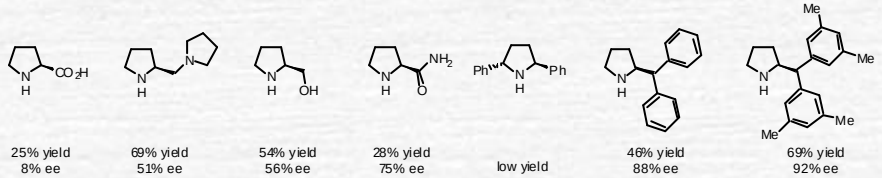
Further into the mechanism



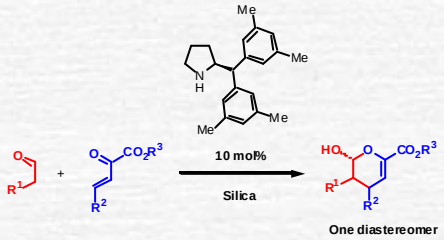
Screening of catalysts







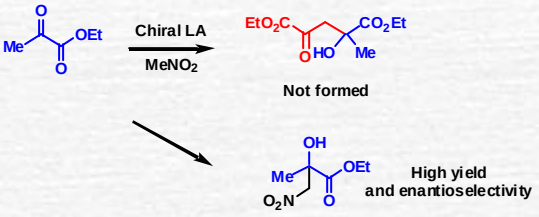
Potential of the reaction



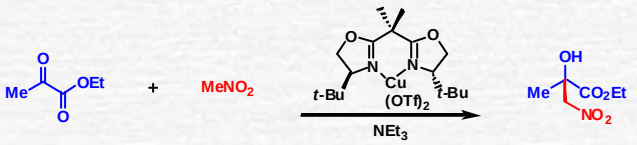
R^1	R^2	R^3	Yield [%]	ee [%]
Et	Ph	Me	50	88
i-Pr	Ph	Me	93	89
Bn	Ph	Me	70	81
Et	4-ClPh	Me	79	85
i-Pr	4-ClPh	Me	70	90
i-Pr	Me	Et	75	94

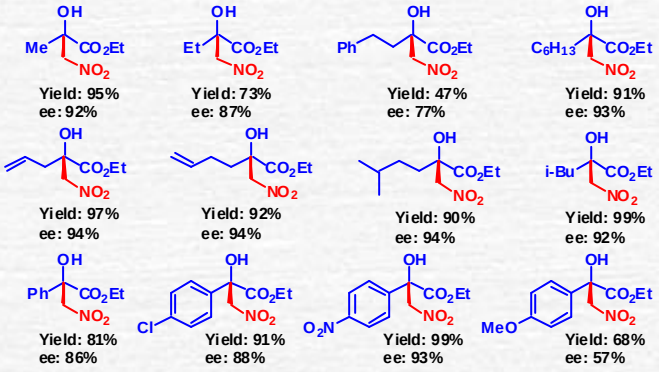
Catalytic asymmetric Henry reactions

a simple approach to optically active b-nitro and b-amino a-hydroxy carboxylic acids



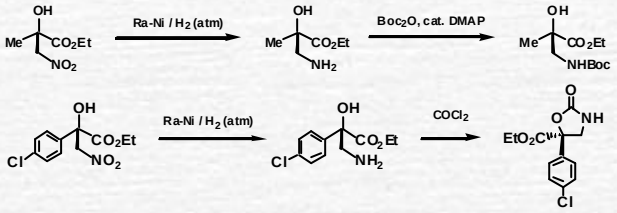
Catalytic Enantioselective Henry Reaction of 2-Keto Esters



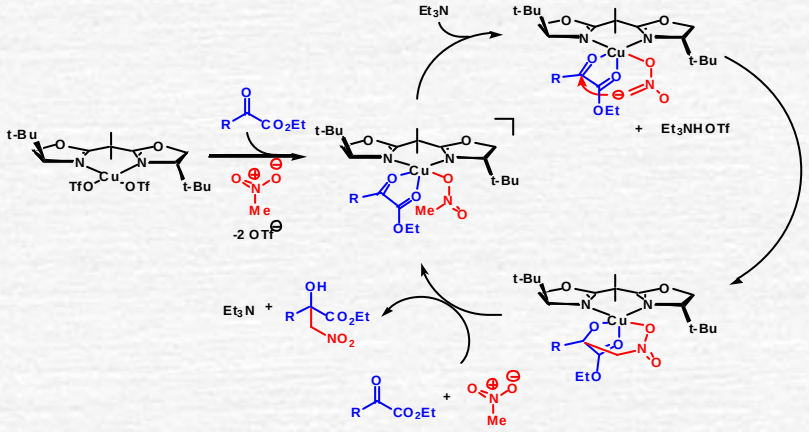


Chem. Commun. **2001**, 2222
J. Org. Chem. **2002**, *67*, 4875

Reduction of nitro functionality

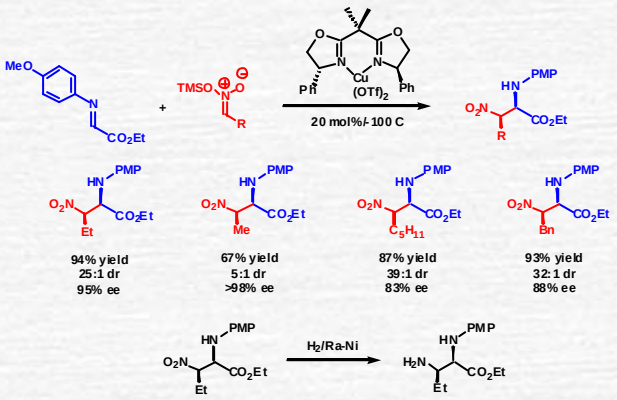


Proposed mechanism



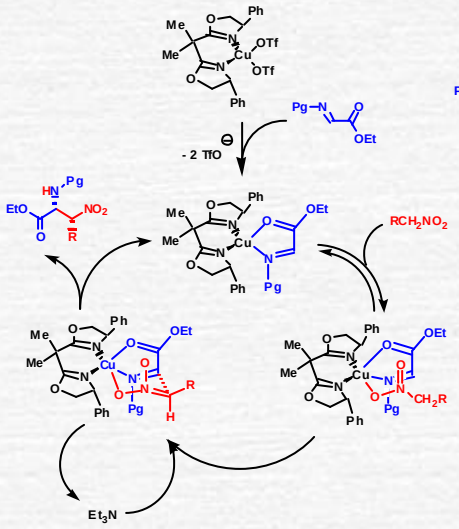
The catalytic enantioselective aza-Henry reaction

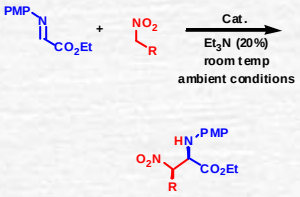
a simple approach to optically active b-nitro and b-amino a-amino carboxylic acids



J. Am. Chem. Soc. **2001**, *123*, 5843

The catalytic asymmetric nitro-Mannich reaction





R = H: 38% yield, 97% ee
R = Me: 61% yield, 7:3 dr, 99% ee
R = Et: 81% yield, 95:5 dr, 97% ee
R = Pentyl: 52% yield, 93:7 dr, 97% ee
R = Bn: 80% yield, 95:5 dr, 95% ee
R = Ph: 59% yield, 55:45 dr, 74% ee

Angew. Chem. Int. Ed. **2001**, *40*, 2992

Acknowledgements

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Mauro Marigo	Nagatoshi Nishiwaki
Tine Risgaard	Mark Roberson
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